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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/512,094	10/21/2004	Mauro Marzi	2818-224	8572

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EXAMINER	
AULAKH, CHARANJIT	
ART UNIT	**PAPER NUMBER**
1625	

MAIL DATE	DELIVERY MODE
05/10/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/512,094	MARZI ET AL.	
	Examiner	Art Unit	
	Charanjit S. Aulakh	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21 and 23-27* is/are rejected.

7)☒ Claim(s) *22* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. According to paper filed on April 10, 2007, the applicants have filed a RCE, canceled claims 1-20 and furthermore, have added new claims 21-27.

2. Claims 21-27 are now pending in the application.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claim 25 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using pharmaceutical composition containing instant compounds of claim 21 alone, does not reasonably provide enablement for using pharmaceutical composition containing instant compounds of claim 21 in combination with any other anticancer drug .The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The following eight different factors (see Ex parte Foreman, 230 USPQ at 547; Wands, In re, 858.F. 2d 731, 8 USPQ 2d 1400, Fed. Cir. 1988) must be considered in order for the specification to be enabling for what is being claimed:

Quantity of experimentation necessary, the amount of direction or guidance provided, presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability and the breadth of claims. In the instant case, the specification is not enabling based on atleast

four of the above mentioned eight different factors such as quantity of experimentation necessary, the amount of direction or guidance provided, presence of working examples, the state of the prior art, unpredictability and the breadth of claims.

The specification teaches cytotoxic activity of instant compounds using lung cancer cell line (NCI-H460) as shown on pages 14 and 15. Based on these teachings, the instant compounds will have utility in treating lung tumors. There is no teaching either in the specification or in prior art that any known anticancer drug in the art having inhibitory effect in lung cancer cell line will maintain or potentiate its anti- tumor effect in the presence of additional every known anticancer drug in the art. There are hundreds of thousands of anticancer drugs known in the art having diverse mechanisms of action and therefore, there is lot of unpredictability for the outcome of combination treatment. The combination with other anticancer drug may even antagonize the inhibitory effect of instant compounds in lung cancer cell line. There are no working examples present showing inhibitory effect of instant compounds in combination with any known single anticancer drug using lung cancer cell line. The instant compounds of formula (I) encompasses several hundreds of thousands of compounds based on the values of variables R1, R2, R3, A and Y and therefore, in absence of such teachings, guidance and presence of working examples, it would require undue experimentation to demonstrate the effectiveness of instant compounds in combination with hundreds of thousands of other anticancer drugs in lung cancer cell line in vitro and hence their utility for treating lung cancer.

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 21 and 23-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In independent claim 21, the value of variable Y is defined as N+R12R13R14. However, the values of variables R12, r13 and R14 are not defined.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

9. Claim 27 is rejected under 35 U.S.C. 103(a) as being unpatentable over Penco (U.S.Patent 6,242,457) in view of Matsumoto (Bioorg. & Medicin. Chem. Lett., cited on applicants form 1449).

Penco discloses camptothecin derivatives having antitumor activity in lung carcinoma (see table 1 in col. 13). The compounds of formula (I) (see col. 5, lines 1-67 as well as

examples) as well as methods of treatment disclosed by Penco are identical to the instant compounds of formula (I) and methods of treatment except that they differ from the instant compounds in having a hydroxyl group in 20^{th} position instead of an ester group (a prodrug). However, Matsumoto teaches design of water soluble prodrugs of sparingly water soluble drugs by utilizing a spontaneously cleavable linker strategy. For the design of such prodrugs, two auxiliary units, a solubilizing moiety and a self-cleavable spacer, are tandemly linked to the parent drug (see page 605, last paragraph to page 606). Combinations of such solubilizing and self-cleavable moieties are identical to the side chain groups in the instant compounds of formula (I) when both n and m represent 1. Although, the prodrug strategy by Matsumoto has been exemplified with an HIV protease inhibitor, the document leaves no doubt regarding general applicability of this approach for preparing prodrugs of compounds with low water solubility (see figure 2 on page 606). Therefore, one skilled in the art would have been motivated to prepare the prodrugs of camptothecin derivatives disclosed by penco using spontaneously cleavable linker strategy disclosed by Matsumoto to enhance water solubility since Penco teaches problem of low water solubility of camptothecin derivatives (see col. 3, lines 58-63) for treating lung carcinoma.

Allowable Subject Matter

10. Claim 22 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Charanjit S. Aulakh whose telephone number is (571)272-0678. The examiner can normally be reached on Monday through Friday, 8:30 A.M. to 5:00 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thomas McKenzie can be reached on (571)272-0670. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

C. S. Aulakh

Charanjit S. Aulakh
Primary Examiner
Art Unit 1625